# Points to Consider for Hematology Quality Control Materials

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Office of Device Evaluation

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While this guidance document represents a final document, comments and suggestions may be submitted at any time for Agency consideration by writing to Dr. Joseph Hackett, Associate Director, Division of Clinical Laboratory Devices, 2098 Gaither Road, HFZ-440, Rockville, MD 20850. For questions regarding the use or interpretation of this guidance, contact Dr. Joseph Hackett at (301) 594-3084.

**U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**Public Health Service**
**Food and Drug Administration**
**Center for Devices and Radiological Health**

Points to Consider for Hematology Quality Control Mixtures

This guidance document represents the agency's current thinking on points to consider for hematology quality control mixtures. It does not create any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulation or both.

This document is an adjunct to the CFR and to FDA Publication Number 87-4224, the manual entitled: In Vitro Diagnostic Devices: Guidance For The Preparation of 510(k) Submissions. It is not to supersede these publications, but is to provide additional guidance and clarification concerning information needed so that the FDA can clear hematology quality control mixtures for marketing. The FDA can make more informed decisions based on a uniform data base, which will lead to greater reproducibility in quality control products. This will additionally result in more reliable quality control mixtures, both analytically and clinically, for use with in vitro diagnostic (IVD) hematology devices (assays/test systems).

The 510(k) premarket notification submission includes evidence that the proposed hematology device (quality control mixture) is substantially equivalent to a predicate device legally marketed in the United States.

**DEFINITION:**

A hematology quality control mixture is a device used to ascertain the accuracy and precision of manual, semiautomated, and automated determinations of cell parameters such as white blood cells (WBC), red blood cells (RBC), platelets (PLT), hematocrit (HCT), hemoglobin (HGB), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC). For purposes of this document, the red blood cell parameter includes reticulocytes, (the immature red blood cells).

These assayed quality control mixtures may contain singular or multiple assay components and are intended to monitor and evaluate the precision and accuracy of hematological test systems. They may be used to detect and estimate systematic and/or random analytical deviations resulting from reagent or instrument defects, or operator variation. An assayed quality control mixture may also be used for internal and/or external laboratory quality control programs.

**PRODUCT CODE(S):**

| | |
|---|---|
| GGM | Control, Hemoglobin |
| GJP | Control, Platelet |
| GJR | Control, Cell Counter, Normal and Abnormal |
| GLK | Control, Hematocrit Control, Red Cell |
| GGL | Control, White Cell |
| GLQ | Control, White and Red Cell (and Reticulocyte) Indices, Mixtures |
| JPK | Control, Hematology Quality, Mixtures |

**REGULATION NUMBER:**

21 CFR § 864.8625 Hematology Quality Control Mixture

(a) Identification. A hematology quality control mixture is a device used to ascertain the accuracy and precision of manual, semiautomated, and automated determinations of cell parameters such as white cell count (WBC), red cell count (RBC), platelet count (PLT), hemoglobin, hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC).

(b) Classification. Class II (performance standards).

**PANEL:** Hematology (81)

**REVIEW REQUIRED:** 510(k)

## I. BACKGROUND

Quality control for the clinical laboratory is a system for assessing the quality of analytical performance. Hematology samples analyzed for this purpose are quality control mixtures. With technological progression, these quality control mixtures have become more complex. In an effort to reduce costs and increase convenience, various cell components are combined for analysis by diverse methodologies, such as centrifugal, conductance, impedance, photo-optical and spectrophotometric. Synthetic constituents are commonly used to increase product stability and protect laboratory personnel from exposure to infectious agents. Matrix expanders, preservatives, antimicrobials, and clarifying agents may also be added to enhance the properties of a quality control mixture.

Hematology quality control mixtures were originally composed of human fresh whole blood. Their instability, however, made them impractical for prolonged use in the clinical laboratory.

Whole blood is a suspension of cellular matter, and deteriorates with time/temperature increases. This leads to considerable changes in cell morphology and other characteristics, which can affect both the accuracy and precision of measurements. [1]

These limitations led to the introduction of commercial whole blood preparations. These were produced by the addition of chemical stabilizers to fresh whole blood controls. Further developments led to the use of artificial and animal blood preparations. These control products displayed even greater stability as compared to fresh whole blood. The validation of these whole blood surrogates was performed with the use of secondary standards that are traceable to human whole blood reference standards.

Whole blood reference standards are used to calibrate automated hematology analyzers, and were established using manual hematology reference methods. These methods were developed according to the recommendations of the International Committee for Standardization in Hematology (ICSH), and are used to assure the accuracy and reproducibility (precision) of the quality control mixture in question. Acceptable reference standards are also available from the World Health Organization (WHO) and the Standards Committee of the College of American Pathologists (CAP). [2-6]

Erratic behavior of quality control mixtures can result in the failure to detect an IVD system error and contribute to the reporting of incorrect patient results. Every attempt should be made to address these concerns with analytical data on the performance of new or modified quality control mixtures when submitting a premarket notification.

## II. DEVICE DESCRIPTION:

Most hematology quality control mixtures are liquid in nature and contain various constituents. These constituents can result in unpredictable interactions, instability, or solution effects when an assay is run. For example, a new biological or synthetic component may affect the behavior of the quality control mixture in a given assay. Additionally, the physical properties of the quality control mixture may be significantly altered by the manufacturing process. Products from new animal sources may exhibit different properties and activity, and may not be uniform over the entire dynamic range of the assay.

Hematology quality control mixtures may contain artificial constituents in a variety of matrices, both human and non-human, that are demonstrated to be substantially equivalent to human fresh whole blood controls.

Assayed quality control mixtures have analyte values assigned to them by the manufacturer, determined through the use of appropriate analytical methods or procedures. Target ranges are presented in the product labeling with given tolerances for specific system applications. These ranges and assigned values are clinically relevant and may be set at or near medical decision levels. Some products classified as hematology quality control mixtures are intended for use as

unassayed controls and may be used as calibration verification (linearity) controls. [7] This document, however, does not address calibrators. Although unassayed controls have no assigned value ranges for components, and system applications may not be specified, target concentrations may be indicated in the labeling, (e.g., low, high, normal). These unassayed controls are also subject to Good Manufacturing Practices (GMP) requirements.

Quality control materials are used in many types of diagnostic assays, and therefore have different analytical considerations to be evaluated. Stability, homogeneity, matrix effects, sensitivity to analytical problems, reproducibility of assigned values, variety and quantity of constituents are important characteristics of all assayed quality control materials.

## III. PERFORMANCE CHARACTERISTICS:

For the assessment of the substantial equivalence of assayed hematology quality control mixtures, the inclusion of the following information in the 510(k) premarket notification is recommended:

A. A description of how the control is prepared during manufacturing; information on the source (i.e., human, animal, or synthetic) and certification that the animal/human source components are safe*; the composition and characteristics of all components; a list of all preservatives or clarifiers contained in the control mixture; and information on the volumes, concentrations, and particle sizes of all applicable components.

   * Safety of animal/human source components is normally satisfied through the use of certified agricultural (animal) facilities or licensed blood centers. Human blood/tissue products are commonly tested with FDA approved methods for several infectious agents (e.g., HBsAg, HBcAb, HIV, HTLV, etc.).

B. The protocol that was followed during the range determination process, including a description of the analytical methods, specific instrument applications, the number of replicate runs and instruments used; the statistical analyses by which the assayed/assigned values and ranges were established; rates of successes/failures; coefficients of variation/standard deviations; and inclusion of independent controls with each value determination run in order to validate the results. [7-8]

C. For FDA files, a description summarizing how open and closed stability of the control has been established. The term "closed" refers to shelf life stability whereas "open" refers to reconstituted or opened conditions. The performance of real time or accelerated studies for substantiation of stability claims is recommended.

D. A description of the characterization of the measurement bias of quality control mixtures containing non-human components. This description is dependent on how new the mixture is, and how well its performance is understood.

E. Representative assigned values for each parameter and level, and for each method application.

## IV. SPECIAL CONSIDERATIONS:

Recommendations:

A. That the formulation and concentrations of quality control mixtures be such that levels for each parameter challenge the medical decision range for that parameter.

B. That the manufacturer regard as modifications: 1) added parameters beyond those of the originally cleared product, and 2) significant changes made in the biological or artificial constituents. These modifications would result in a new 510k.

C. That future claims for additional instrument applications with a determination of their respective control values/ranges be the responsibility of the manufacturer; and that records of the same performance characteristics described above be kept on file for each new application added.

Additional considerations are:

D. If a distributor is simply placing their label on an already cleared product, without changing the product or labeling in any way, a 510(k) is not needed. See 21 CFR § 807.85 for additional information.

E. Analytes present in a quality control mixture which do not have an FDA cleared (Class I or Class II) or approved assay (Class III), may list assigned values only if these values are clearly designated in the labeling as being "For Investigational Use Only" or "For Research Use Only"**. Because these parameters have not been FDA cleared or approved for clinical use, they are not for use in clinical decision-making.

** As stated in the labeling requirements for <u>in vitro</u> diagnostic devices, performance characteristics of investigational devices have not been established; and research devices are not for use in diagnostic procedures.

## V. LABELING CONSIDERATIONS:

The manufacturer should assure that for a new device, labeling complies with Section 502(a) of the Act in that the Directions For Use are adequate, and not false or misleading. 21 CFR 801.119 states, "A product intended for use in the diagnosis of disease and which is an *in vitro* diagnostic product as defined in §809.3(a) of this chapter shall be deemed to be in compliance with the

requirements of 502(a) and 502(f)(1) of the act if it meets the requirements of §809.10, Labeling for *in vitro* diagnostic products." The emphasis of this Points to Consider document is to discuss and explain some of the points in the above publications.

All abbreviations and acronyms used by the manufacturer in the labeling should be clear and well defined. The following information should be included in the labeling, in the order and format presented:

A. Package Insert Labeling

1. Intended Use(s)

Provide a concise description of the essential information about the product including the following information:

a. the name of the product.

b. the components or constituents and whether it is a single or multiple parameter control.

c. the control matrix base or type, e.g., whole blood, plasma, etc.

A typical Intended Use statement is as follows: "ABC's Control is a quality control material for use in assessing accuracy and precision of hematology analyzers."

2. Summary and Explanation

a. provide a description of the function of quality control testing and/or the quality control program.

b. provide summary of how the control product is prepared and how target ranges are established.

3. Contents

The following should be provided as appropriate:

a. universal precautions or biohazard warning for animal/human blood products or tissue; and a statement that the quality control mixture has been tested, with FDA approved methods, for human infectious agents such as HBsAg, HBcAb, HCV, HIV-1/2, HTLV-1, etc.

b. any indication of instability or deterioration.

4. Test Procedure or Directions for Use

The following information should be provided as appropriate:

a. step-by-step instructions, e.g., for reconstitution, mixing, or dilution.

b. a recommendation concerning the interpretation of results, or a referral of the user to the quality control guidelines established within their laboratory.

c. statement of purification/treatment required for use.

5. Assay Values/Ranges

The labeling should indicate a list of the mean(s) and range(s), including the standard deviation(s), for each instrument or method application(s).

6. Bibliography

## VI. REFERENCES:

1. Inhorn, Stanley L., MD, Editor. Quality Assurance Practices for Health Laboratories, "Hematology", pp. 687-744, American Public Health Association, Washington, DC, 1978.

2. *National Committee for Clinical Laboratory Standards (NCCLS), Procedure for Determining Packed Cell Volume by the Microhematocrit Method-Second Edition; Approved Standard (1994), Document H7-A2.

3. *NCCLS, Reference and Selected Procedures for the Quantitative Determination of Hemoglobin in Blood-Second Edition; Approved Standard (1994), Document H15-A2.

4. NCCLS, Reference Leukocyte Differential Count (Proportional) and Evaluation of Instrumental Methods; Approved Standard (1992), Document H20-A.

5. NCCLS, Performance Goals for the Internal Quality Control of Multichannel Hematology Analyzers; Approved Standard (1996), Document H26-A.

6. NCCLS, Reticulocyte Counting by Flow Cytometry; Proposed Guideline (1993),

Document H44-P.

7. NCCLS, Evaluation of the Linearity of Quantitative Analytical Methods; Proposed Guideline (1986), Document EP6-P.

8. NCCLS , Precision Performance of Clinical Chemistry Devices, Second Edition, Tentative Guideline (1992), Document EP5-T2.

9. Lewis, SM and Koepke, JA. Hematology Laboratory Management and Practice, Butterworth-Heinemann, Ltd., 1995.

*American National Standard

**Review Checklist**

- ☐ Description of the product
- ☐ Assigned range (protocols)
- ☐ Stability Information (opened & closed)
- ☐ Matrix bias
- ☐ Assay sheet

Labeling

- ☐ Proprietary Name and Established or Common Name
- ☐ Intended Use
- ☐ Summary & Explanation
- ☐ Contents
- ☐ Directions for Use
- ☐ Limitations
- ☐ Assay Values/Ranges/Assay Sheets
- ☐ Bibliography
- ☐ Name and Place of Business of Manufacturer, Packer, or Distributor
- ☐ Date of last labeling revision